We claim:

1. A method for identifying constitutively activating mutations in a receptor or an ion channel, comprising:

    (A) providing a library of coding sequences for potentially activating mutations of a candidate receptor or ion channel, which library is generated by replacing coding sequences for small or medium side-chain amino acids with coding sequences for large side-chain amino acids, wherein said small or medium side-chain amino acids are located in or proximate transmembrane segment(s) of the receptor or ion channel;

    (B) expressing said library in host cells;

    (C) measuring the activity of the encoded receptor or ion channels in said host cells;

    (D) identifying those coding sequence(s) which encoded activated receptors or ion channels.

2. The method of claim 1, wherein the receptor is selected from the group consisting of: a growth factor receptor, a cytokine receptor, a chemokine receptor, and an multisubunit immune recognition receptor (MIRR).

3. The method of claim 1, wherein the receptor is an orphan receptor.

4. The method of claim 1, wherein the receptor is a multipass transmembrane receptor.

5. The method of claim 4, wherein the receptor is a 7TM receptor selected from the group consisting of: a G-protein coupled receptor, a chemoattractant peptide receptor, a neuropeptide receptor, a light receptor, a neurotransmitter receptor, and a polypeptide hormone receptor.

6. The method of claim 1, wherein the receptor is a receptor tyrosine kinase (RTK).

7. The method of claim 1, wherein the ion channel is a ligand gated ion channel.

8. The method of claim 1, wherein the activity is measured directly by determining the level of second messengers generated in response to receptor or ion channel activation.

9. The method of claim 1, wherein the activity is measured indirectly via an indicator gene.

10. The method of claim 9, wherein the indicator gene is an unmodified endogenous gene.

11. The method of claim 9, wherein the indicator gene is a heterologous reporter gene, the activation of the transcriptional regulatory element of which is directly or indirectly regulated by the receptor or ion channel.

12. The method of claim 10 or 11, wherein the level of transcriptional activation of the indicator gene is amplified by overexpressing one or more intermediate components of the signaling cascade leading to the activation of the indicator gene.

13. The method of claim 9, wherein the sensitivity of the indicator gene is modified by manipulating the promoter sequence at the natural locus for the indicator gene.

14. The method of claim 9, wherein the activity of the indicator gene is modified by manipulating the transcriptional regulatory sequence at the natural locus for the indicator gene.

15. The method of claim 9, wherein the activity of the indicator gene is modified by replacing the transcriptional regulatory sequence of the endogenous indicator gene with that of a heterologous gene.

16. The method of any one of claim 11, 14, or 15, wherein the transcriptional regulatory element is derived from that of immediate early genes.

17. The method of any one of claim 11, 14, or 15, wherein the transcriptional regulatory element is derived from several heterologous genes.

18. The method of claim 11, wherein the reporter gene encodes a gene product selected from the group consisting of: chloramphenicol acetyl transferase, beta-galactosidase, secreted

alkaline phosphatase, a gene product which confers a growth signal, and a gene product for growth in media containing aminotriazole or canavanine.

19. The method of claim 1, wherein the small or medium side-chain amino acids are located at the interfaces between transmembrane helices.

20. The method of claim 1, wherein the small or medium side-chain amino acids are selected from the group consisting of: glycine, alanine, and serine.

21. The method of claim 1, wherein the small or medium side-chain amino acids are selected from the group consisting of: asparagine, aspartic acid, cysteine, proline, threonine and valine.

22. The method of claim 1, wherein the large/bulky side-chain amino acids are selected from the group consisting of: tryptophane, leucine, histidine, threonine, and tyrosine.

23. The method of claim 1, wherein the large side-chain amino acids are selected from the group consisting of: asparagine, cysteine, glutamine, isoleucine, methionine, phenylalanine, proline, and valine.

24. The method of claim 1, wherein the cell is a prokaryotic cell.

25. The method of claim 1, wherein the cell is a eukaryotic cell.

26. The method of claim 1, wherein the cell is a mammalian cell.

27. The method of claim 25, wherein the cell is selected from the group consisting of: an avian cell, an insect cell, a yeast cell, and a plant cell.

28. The method of claim 25, wherein the cell is a pigment cell capable of dispersing or aggregating its pigment in response to an activated receptor or ion channel.

29. The method of claim 1, wherein the mutation is identified as an activating mutation if the activity of the mutant polypeptide increases by at least 2-fold when compared to the activity of the wild-type polypeptide.

30. The method of claim 1, wherein the mutation is identified as an activating mutation if the activity of the mutant polypeptide increases by at least 5-fold when compared to the activity of the wild-type polypeptide.

31. The method of claim 1, wherein the mutation is identified as an activating mutation if the activity of the mutant polypeptide increases by at least 10-fold when compared to the activity of the wild-type polypeptide.

32. A method for identifying constitutively activating mutations in a multipass transmembrane receptor, comprising:

    (A) providing a library of coding sequences for a multipass transmembrane receptor, which library includes variant sequences which differ from the wild-type sequence of the receptor by one or more point mutations in or proximate a transmembrane segment(s) of the receptor that replace a small or medium amino acid residue with a large amino acid residue;

    (B) expressing said library in host cells;

    (C) measuring the activity of the encoded multipass transmembrane receptor in said host cells;

    (D) identifying those coding sequence(s) which encoded activated multipass transmembrane receptor.

33. A method for identifying a target second messenger or downstream signaling component of a receptor or ion channel, comprising:

    (A) identifying an activating mutation of a receptor or ion channel using the method of claim 1;

    (B) expressing said activating mutation of a receptor or ion channel in host cells; and,

    (C) identifying one or more second messenger molecules or downstream signaling components whose level is higher or lower or which is modified as a consequence to expression of said activating mutation of said receptor or ion channel.

34. The method of claim 33, wherein the receptor is selected from the group consisting of: a growth factor receptor, a cytokine receptor, a chemokine receptor, and an multisubunit immune recognition receptor (MIRR).

35. The method of claim 33, wherein the receptor is a multipass transmembrane receptor.

36. The method of claim 35, wherein the receptor is a 7TM receptor selected from the group consisting of: a G-protein coupled receptor, a chemoattractant peptide receptor, a neuropeptide receptor, a light receptor, a neurotransmitter receptor, and a polypeptide hormone receptor.

37. The method of claim 33, wherein the receptor is a receptor tyrosine kinase (RTK).

38. A method for identifying an antagonist of an activating mutation of a receptor or ion channel, comprising:

    (A)   translationally providing a constitutively active mutant of a receptor or ion channel in an environment, which active mutant includes one or more point mutation(s) in or proximate a transmembrane segment(s) of the receptor that replace a small or medium amino acid residue with a large amino acid residue;

    (B)   contacting the receptor or ion channel with a test agent;

    (C)   comparing the activity of the receptor or ion channel in the presence of the test agent with the activity of the receptor or ion channel in the absence of the test agent; and,

    (D)   identifying the test agent as an antagonist of the activated receptor or ion channel if the activity of the receptor or ion channel in the presence of the test agent is lower than the activity of the receptor or ion channel in the absence of the test agent.

39. The method of claim 38, wherein the translationally providing step is performed in a cell.

40. The method of claim 39, wherein the cell is a prokaryotic cell.

41. The method of claim 39, wherein the cell is a eukaryotic cell.

42.   The method of claim 41, wherein the cell is selected from the group consisting of: a mammalian cell, an avian cell, an insect cell, a yeast cell, and a plant cell.

43.   The method of claim 41, wherein the cell is a pigment cell capable of dispersing or aggregating its pigment in response to an activated receptor or ion channel.

44.   The method of claim 38, wherein the test agent is a member of a library.

45.   The method of claim 44, wherein the library is selected from the group consisting of: a randomly synthesized polypeptide library, a semi-randomly synthesized polypeptide library, a cDNA encoded polypeptide library, a genomic DNA encoded polypeptide library, a synthetic chemical library, and a natural chemical compound library.

46.   A method for generating a non-human transgenic animal which expresses at least one activating mutant(s) of a receptor or an ion channel, comprising the steps of:

   (A)   identifying an activating mutant of a receptor or an ion channel using the method of claim 1; and,

   (B)   generating a non-human transgenic animal expressing said activating mutant.

47.   The method of claim 46, wherein the transgenic animal is selected from the group consisting of: a mammal, an insect, and a yeast.

48.   A method for identifying a modulator of a receptor or ion channel, comprising:

   (A)   identifying an activating mutation of a receptor or ion channel using the method of claim 1;

   (B)   identifying one or more second messenger molecules or downstream signaling components whose level is higher or lower or which is modified as a consequence to expression of said activating mutation of said receptor or ion channel;

   (C)   contacting an environment expressing a wild-type receptor or ion channel with a test agent;

(D)   comparing the level of target second messenger molecules or down stream signaling components identified in step (B) in the presence or absence of the test agent; and,

(E)   determining whether the test agent increases or decreases the level of the target second messenger.

49.   A method of conducting a pharmaceutical business, comprising:

(A)   by the method of claim 38 or 48, identifying one or more agents which effects signaling by a cell-surface receptor or ion channel;

(B)   conducting therapeutic profiling of said identified agent(s), or further analogs thereof, for efficacy and toxicity in animals; and,

(C)   formulating a pharmaceutical preparation including one or more agents identified in step (B) as having an acceptable therapeutic profile.

50.   The business method of claim 49, further comprising an additional step of establishing a distribution system for distributing the pharmaceutical preparation for sale.

51.   The business method of claim 49 or 50, further including establishing a sales group for marketing the pharmaceutical preparation.

52.   A method of conducting a pharmaceutical business, comprising:

(A)   by the method of claim 38 or 48, identifying one or more agents which effects signaling by a cell-surface receptor or ion channel;

(B)   (optionally) conducting therapeutic profiling of the agent for efficacy and toxicity in animals; and,

(C)   licensing, to a third party, the rights for further drug development of the target agent.